Ovarian Cancer – Facts and Myths

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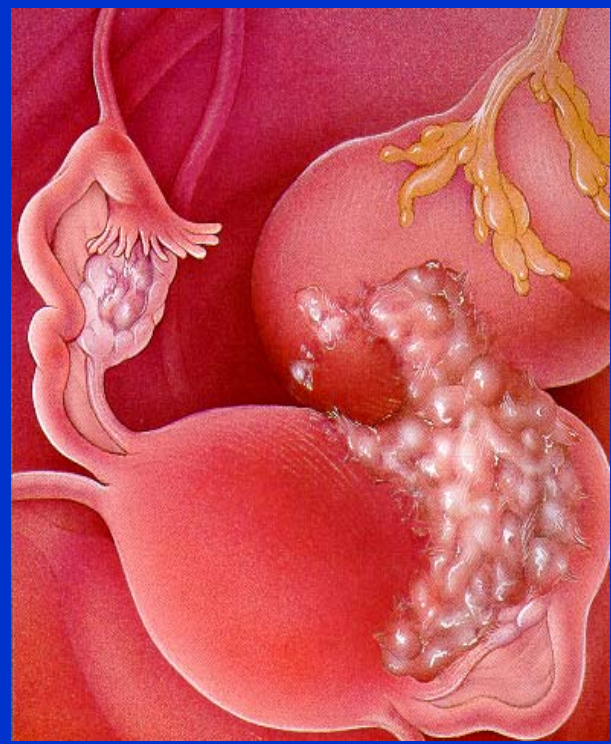


Ovarian Cancer

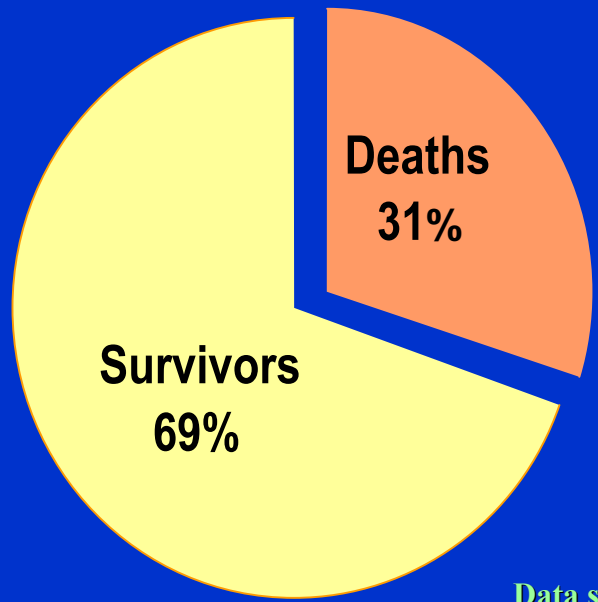
What is ovarian cancer?

- Ovarian cancer arises from cells within the ovary
- Ovarian cancer is the leading cause of death among female genital cancers
- 25,000 new cases /year of ovarian cancer
- 14,500 deaths /year from ovarian cancer

5-Year Survival Rates

Ovarian Cancer

Cervical Cancer



Endometrial Cancer

Data source: NCI Surveillance, Epidemiology and End Results Program, 1997

Ovarian Cancer

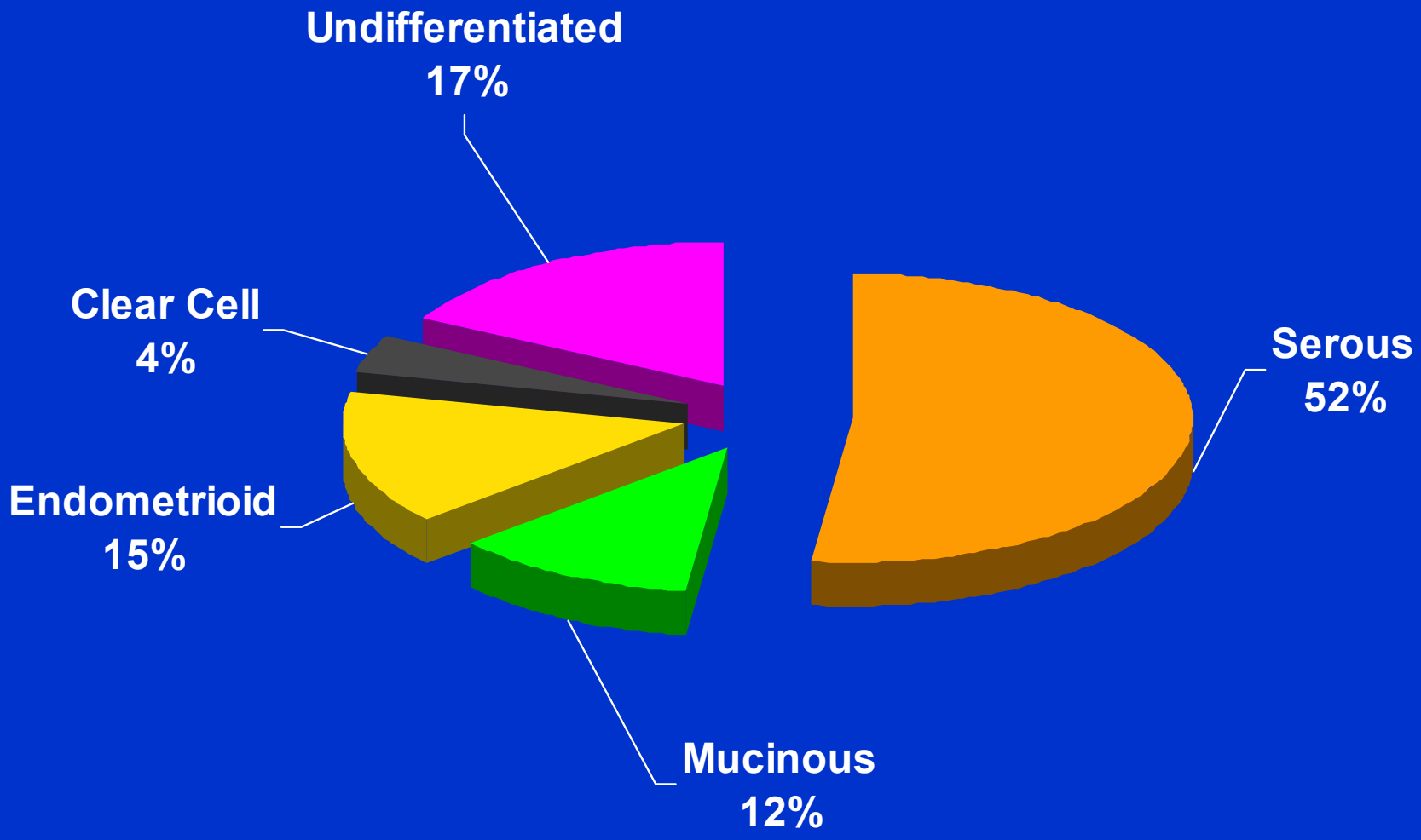
What are the types of ovarian cancer?

- Most ovarian cancer is of the "epithelial" type (outer layer of the ovary)
- Each type of cell in the ovary can give rise to a different kind of cancer

WHO Classification

Class	Approx. Freq. (%)
Epithelial	65
Sex cord-Stromal	6
Lipid cell	<0.1
Germ cell	20-25
Gonadoblastoma	<0.1
Metastatic to ovary	5

Histology of Epithelial Ovarian Cancer



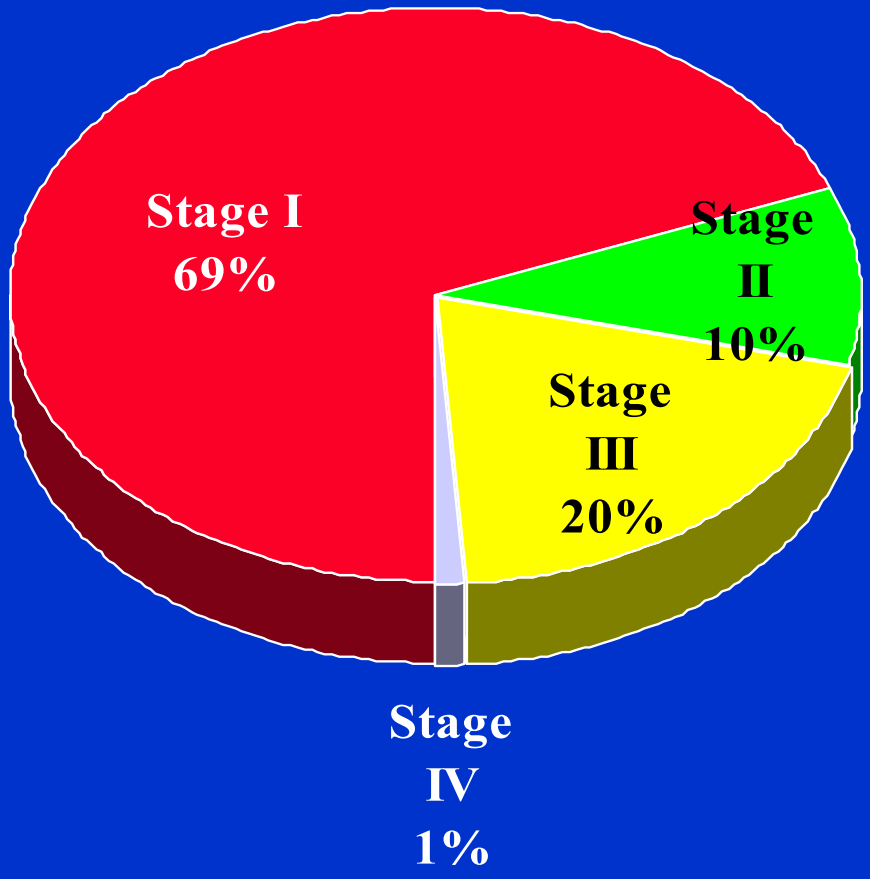
Borderline Ovarian Tumors

AKA – Low malignant potential (LMP)tumors

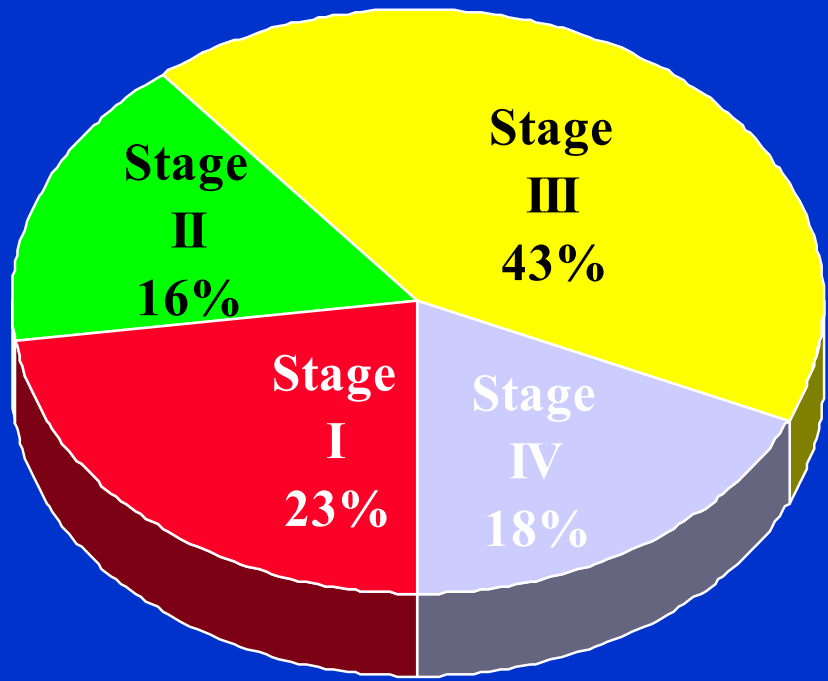
- 15% of epithelial ovarian cancers
- Three-quarters are Stage I
- Slow-growing with infrequent and late recurrences
- Nearly 100% survival in Stage I
- Average age of women between those with benign tumors and those with cancer

Stage Distribution of Ovarian Tumors

LMP Ovarian Tumors



Ovarian Cancer



Ovarian Cancer

Why is ovarian cancer so deadly?

- Most patients with ovarian cancer present with advanced stage disease
- Survival is primarily related to the cancer stage

Ovarian Cancer

- 85% of early stage ovarian cancer patients survive 5 years or longer
- 25% of patients with advanced stage ovarian cancer live 5 years
- 75% of ovarian cancer patients present with advanced stage disease

Ovarian Cancer

Myth: Ovarian cancer doesn't give any symptoms, especially in early stages

Reality: Retrospective surveys of ovarian cancer patients reveal that most had symptoms

- Unfortunately, many symptoms are mild, vague, nonspecific, and misinterpreted by patients and their physicians

Screening Vs. Early Detection

Survey of 1725 women solicited via ovarian cancer newsletter

- 95% had symptoms (abdominal, GI, pain, constitutional, urinary, vaginal)
- Only 11% of Stage I and 3% of Stage III/IV were asymptomatic
- Symptoms commonly ignored by patients
- Delay in diagnosis common (diagnosis > 6 mon - 26%, > 1 yr - 11%)

Goff and Mandel, *SGO*, 2000

Screening Vs. Early Detection

Ovarian cancer survey (cont'd)

- Factors associated with diagnosis delay: omission of pelvic exam, multitude of symptoms, diagnoses of - no problem, depression, stress, IBS, gastritis
- Other factors: US, CT, or CA 125 not obtained; younger age
- Conclusion: majority of women with ovarian cancer are symptomatic, delay in diagnosis common

Goff and Mandel, *SGO*, 2000

Ovarian Cancer

Are there any risk factors?

- Age
- Nulliparity
- Ethnicity (Caucasian)
- Previous endometrial, colon, breast CA
- Family Hx of ovarian CA

Ovarian Cancer

Is ovarian cancer inherited?

- Only 5-10% of ovarian cancer is familial (genetic)
- 90-95% of ovarian cancer is sporadic (non-genetic)
- Most genetic ovarian cancer due to mutations in BRCA 1 & 2 genes

Familial Ovarian Cancer Syndromes

Hereditary factors are likely if:

- Early age of cancer onset (late 30's, early 40's)
- Both ovaries have cancer
- Patients develop multiple cancers (breast, colon, uterine, and others)
- Clustering of cancer cases in an extended family tree

Familial Ovarian Cancer Syndromes

- Important to recognize hereditary predisposition
- Detailed family history is required
- Genetic counseling is helpful
- Establish an extended pedigree to evaluate genetic risk

Familial Ovarian Cancer Syndromes

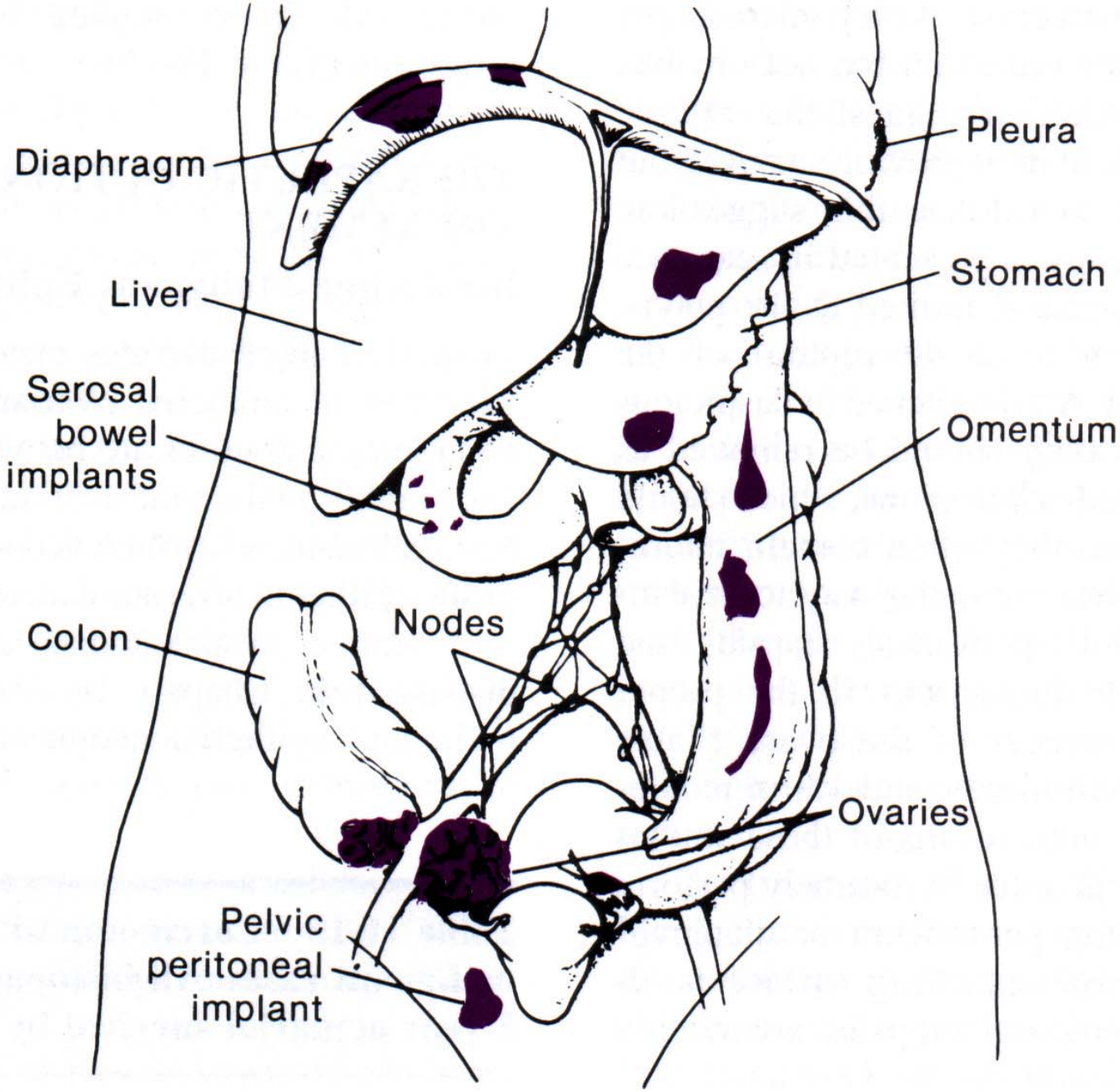
Risks to other family members if someone has ovarian cancer:

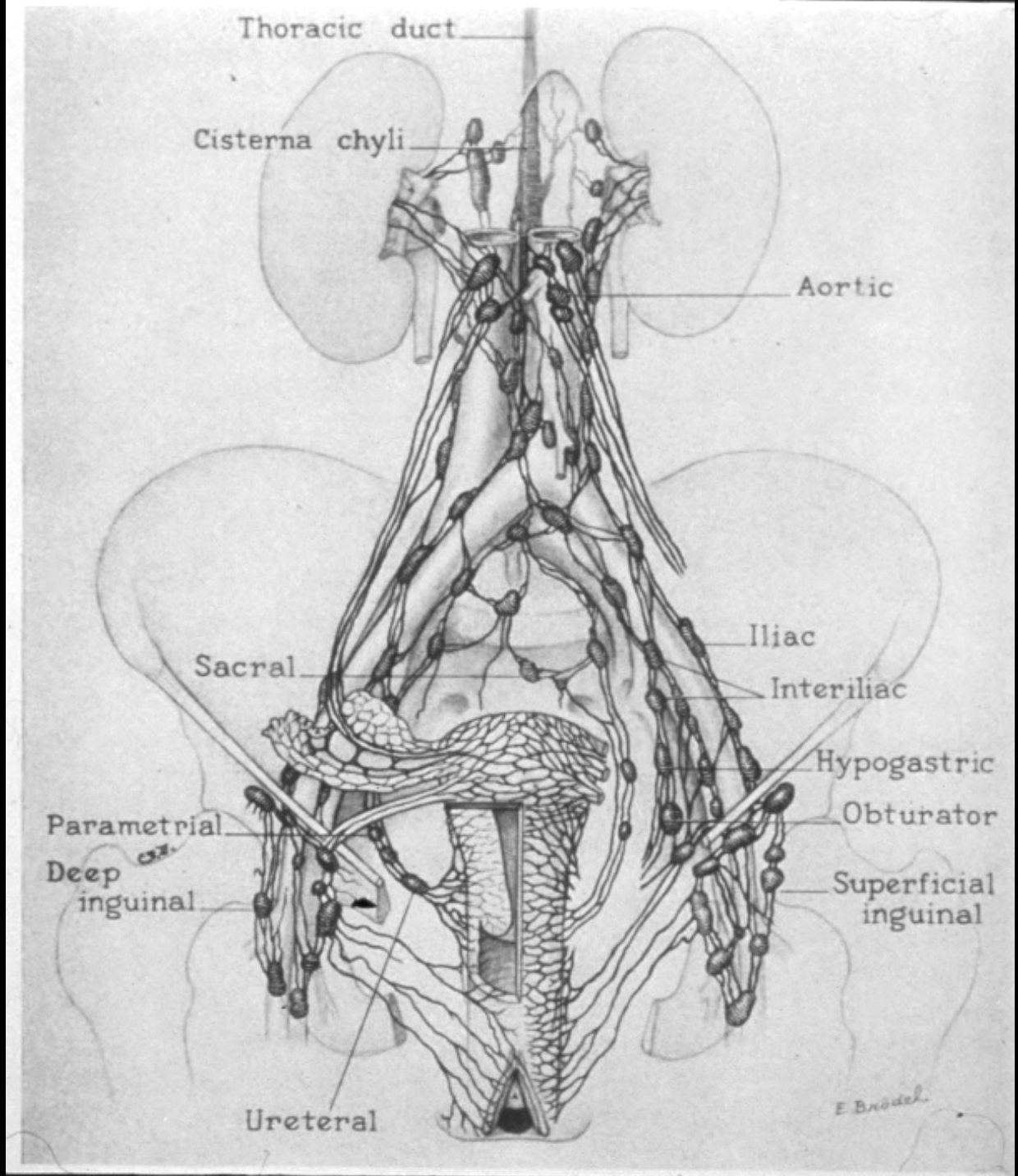
- Baseline lifetime risk - 1.4%
- One first-degree relative - 5%
- Two relatives - 5-10%
- Hereditary ovarian cancer syndrome - 25-50%

Ovarian Cancer

How does ovarian cancer spread?

- Possible routes of spread:
  - Throughout abdominal cavity
  - Through the lymphatic system
  - Into the blood stream
- Each type of ovarian cancer has a distinctive pattern of spread

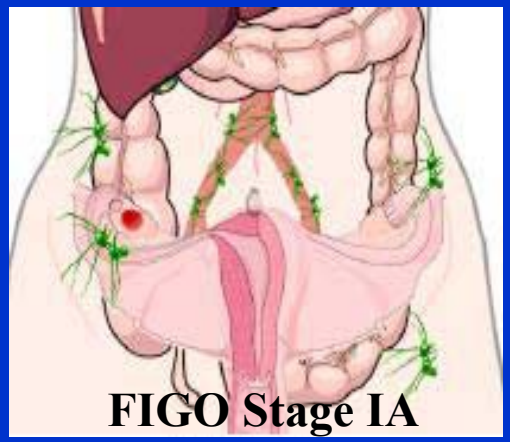

Diaphragm
Pleura
Liver
Stomach
Serosal
bowel
implants
Omentum
Colon
Nodes
Ovaries
Pelvic
peritoneal
implant

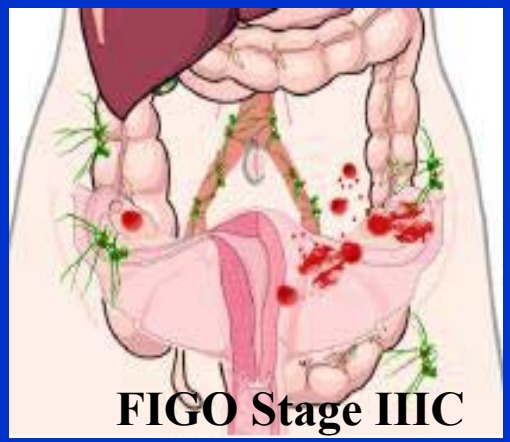

Thoracic duct
Cisterna chyli
Aortic
Iliac
Sacral
Interiliac
Hypogastric
Parametrial
Obturator
Deep inguinal
Superficial inguinal
Ureteral
E. Brödel

Ovarian Cancer

What does cancer stage mean?

- Cancer stage is shorthand way of describing location
- Most cancers are staged according to rules (e.g., FIGO, AJCC, etc.)
- Cancer staging provides information about treatment, prognosis, and comparison of clinical trial


FIGO Stage IA


FIGO Stage IIIC

Ovarian Cancer Staging

- Stage I - cancer confined to one or both ovaries
- Stage II - cancer metastatic to pelvic tissues (uterus, tubes, bladder, sigmoid, etc.)
- Stage III - peritoneal implants outside of pelvis and/or positive nodes (including groins)
- Stage IV - distant mets, + pleural cytology

Ovarian Cancer

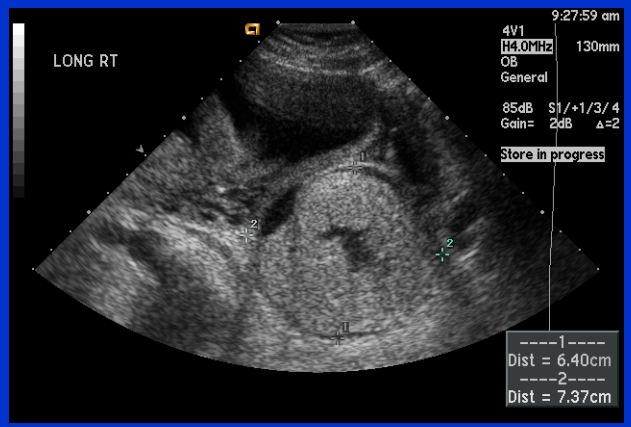
How is the diagnosis made?

- History
- Physical examination
- Imaging tests (ultrasound, CT scans)
- Blood tests

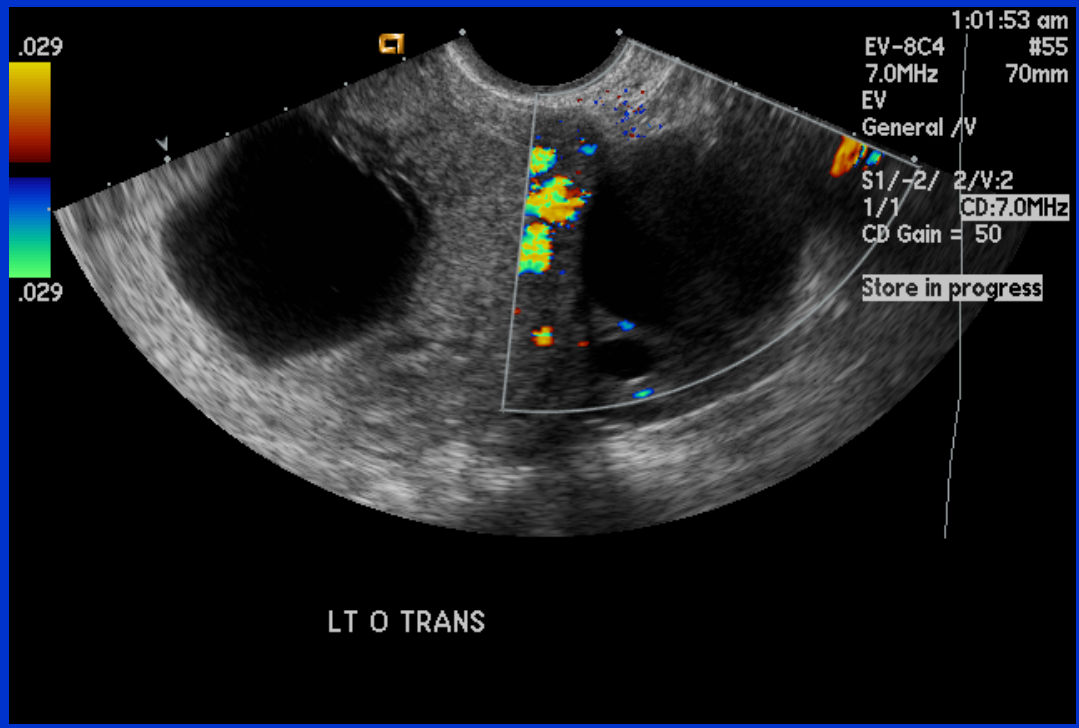
Ovarian Cancer

Ultrasound

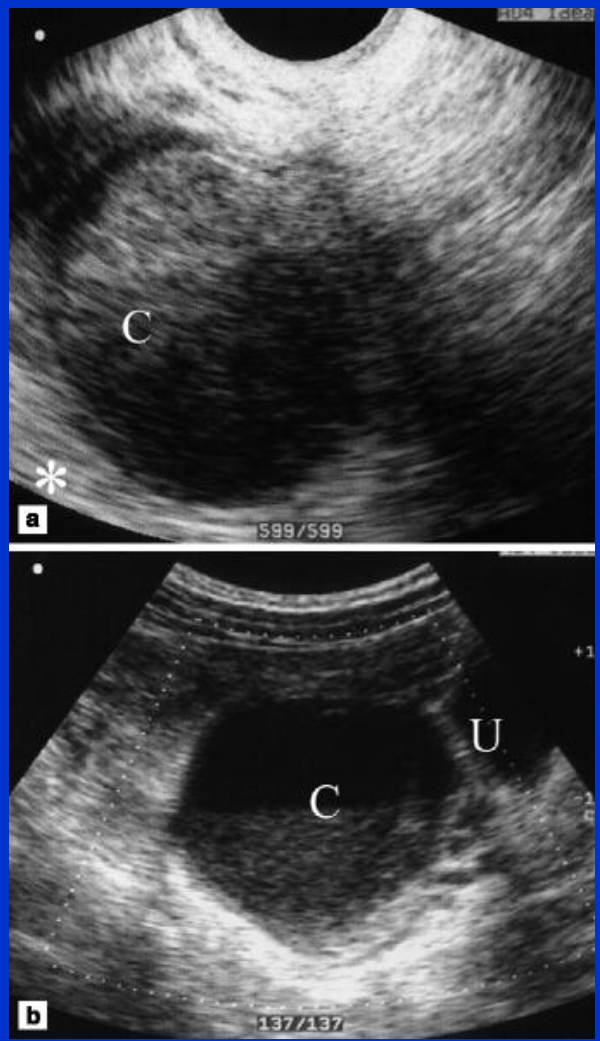
- Good initial test
- Cannot make histologic diagnosis
- Predictive value: malignancy - <50%
- Predictive value: benignity - >90%



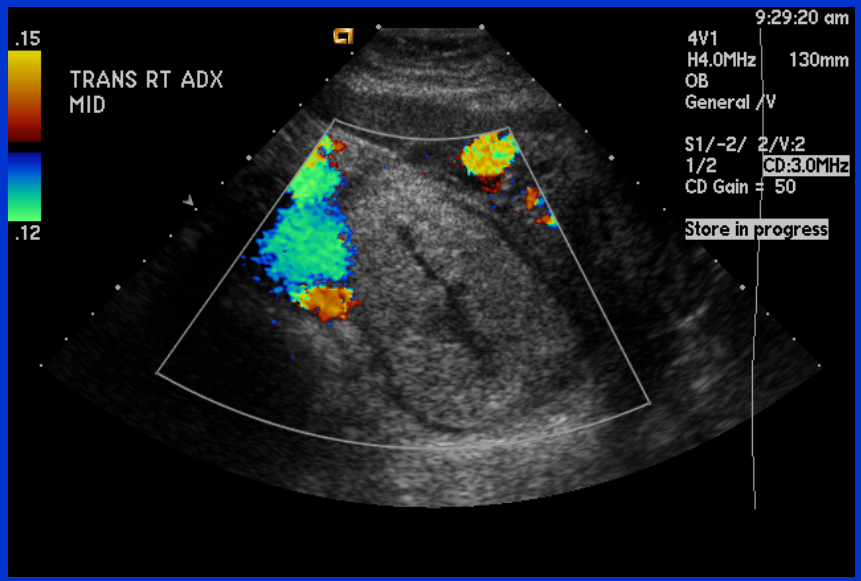
Simple Ovarian Cysts

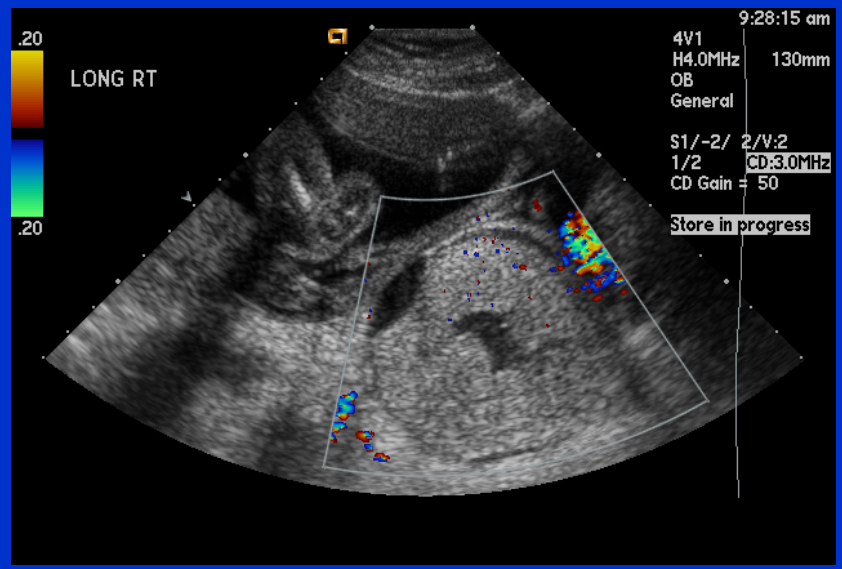


Hemorrhagic Ovarian Cyst



Complex, Solid Ovarian Mass

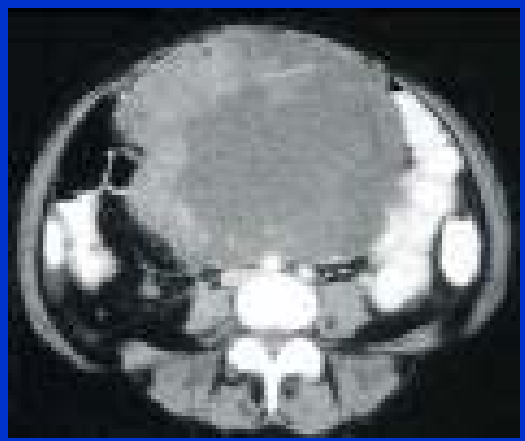


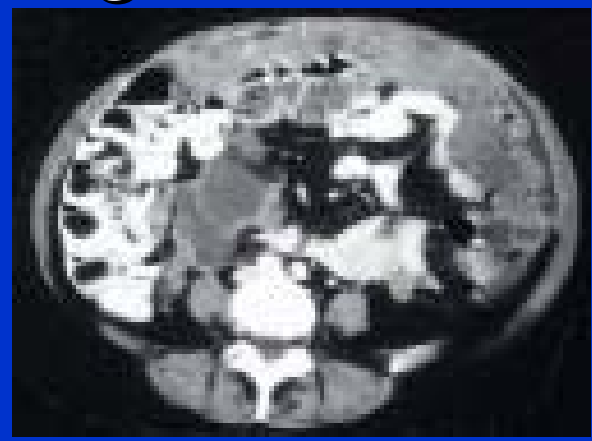


Ovarian Cancer

CT Scan

- Better resolution than ultrasound
- Better characterization of mass
- Useful for estimating stage of cancer
- Cannot make histologic diagnosis





Tests for Ovarian Cancer

Blood tests

- Benefits: convenience, modest cost, minimal expertise needed to perform assay, better patient acceptance
- Potential tests: CA 125, proteomics, glycans analysis

CA 125

- Ovarian surface protein associated with most epithelial ovarian cancers (EOC)
- Elevated in 80-90% of EOC
- Only 50% of Stage I ovarian cancers have elevated CA 125
- Many benign causes of elevated CA 125
- False positive rate of ~ 2% in postmenopausal women

Conditions Associated with Elevated CA 125

Gynecologic

- Adenomyosis
- Cystadenomas
- Ectopic pregnancy
- Endometriosis
- First-trimester pregnancy
- Functional ovarian cysts
- Menstruation
- Ovarian hyperstimulation
- Pelvic inflammatory disease
- Uterine myomas

Nongynecologic

- Colitis
- CHF
- Diabetes
- Hepatitis and other liver disease
- Nonmalignant ascites
- Pancreatitis
- Peritonitis
- Pneumonia
- Renal disease
- Systemic lupus erythematosis

Table 9-5. Serum CA-125 Values Reported for Various Conditions Other Than Advanced Ovarian Carcinoma

Condition	Total	No. Elevated[a]	Mean ± SEM	Highest Value
Endometrioma >4 cm	19	19[b]	53 ± 2	110
Endometriosis	7	0	15 ± 1	—
Nonendometriotic cyst	20	0	11 ± 1	—
Liver cirrhosis				
No ascites	16		43.5 ± 14.2	225
Ascites	24	24	291 ± 29.0	800
Pregnancy (IUP)	17	7[c]	27 ± 6.7	150
Ectopic, intact	10	9	97 ± 9.6	275
Ectopic, ruptured	17	13	84.4 ± 9.4	360
Systemic Lupus				
Active	28	10	48	272
Inactive	9	2	32	132
Meigs syndrome	1	1	—	226
Stage I ovarian carcinoma	13	3	54	70
Pelvic inflammatory disease	30	10	—	550

[a] >35 U/ml except where specified.

[b] Normal <20 U/ml.

[c] Normal <18 U/ml.

(Data are from Bergmann et al [1987], Halila et al [1986], Jones and Surwit [1989], Mann et al [1988], Moncayo and Moncayo [1991], Pittaway et al [1987] and Sadovsky et al [1991].)

CA 125

- Serial collections of serum tested for CA 125
- Rising CA 125 levels occasionally preceded ovarian cancer diagnosis by up to 18 months*
- However, single CA 125 measurement is insensitive
- Serial CA 125 measurements may be more sensitive

*Helzlsouer and Bush, *JAMA,* 1993

Ovarian Cancer

Myth: Annual CA-125 blood tests are a good screening test for ovarian cancer

Reality: There are no currently proven effective screening tests for ovarian cancer

- Screening CA 125 tests have a high false-positive rate (non-specific results), about 2% in postmenopausal women

Ovarian Cancer

Why don't doctors screen for ovarian cancer?

- There are no currently effective methods for screening
- Previous strategies have included:
  - Serial CA 125 blood tests
  - Serial pelvic ultrasound exams
  - Combination of both

Screening for Ovarian Cancer

- Ovarian cancer has low prevalence (30/100,000)
- If test is 80% sensitive and 99% specific, then PPV is only 2.3% (CA 125 in postmenopausal women)
- If prevalence is higher (5/1000 - risk of BRCA 1 carriers) - same characteristics give PPV 28.7%
- Acceptable PPV is about 10%
- If prevalence is low, specificity must be very high (e.g., 99.7%)

Hensley and Castiel, *Oncology* 2000

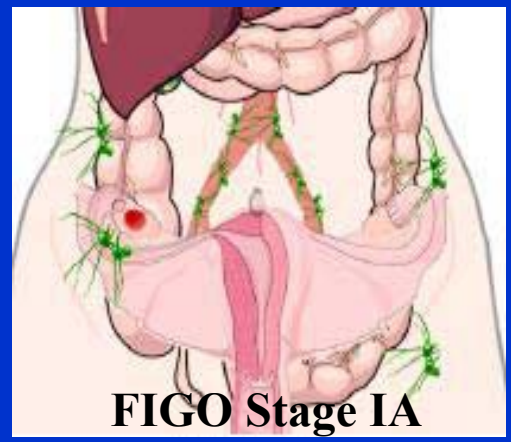
Costs of Ovarian Cancer Screening

- 43 million women > 45 years in U.S.
- Cost of serial annual screening: pelvic US/CA 125 - $14 billion/year
- Cost of $445,177/case Stage I ovarian cancer
- Costs driven by low PPV and expense of surgery
- More cost effective? - Triage of annual CA 125 with US confirmation

Rosenthal and Jacobs, *Sem in Oncol*, 1998

Screening Vs. Early Detection

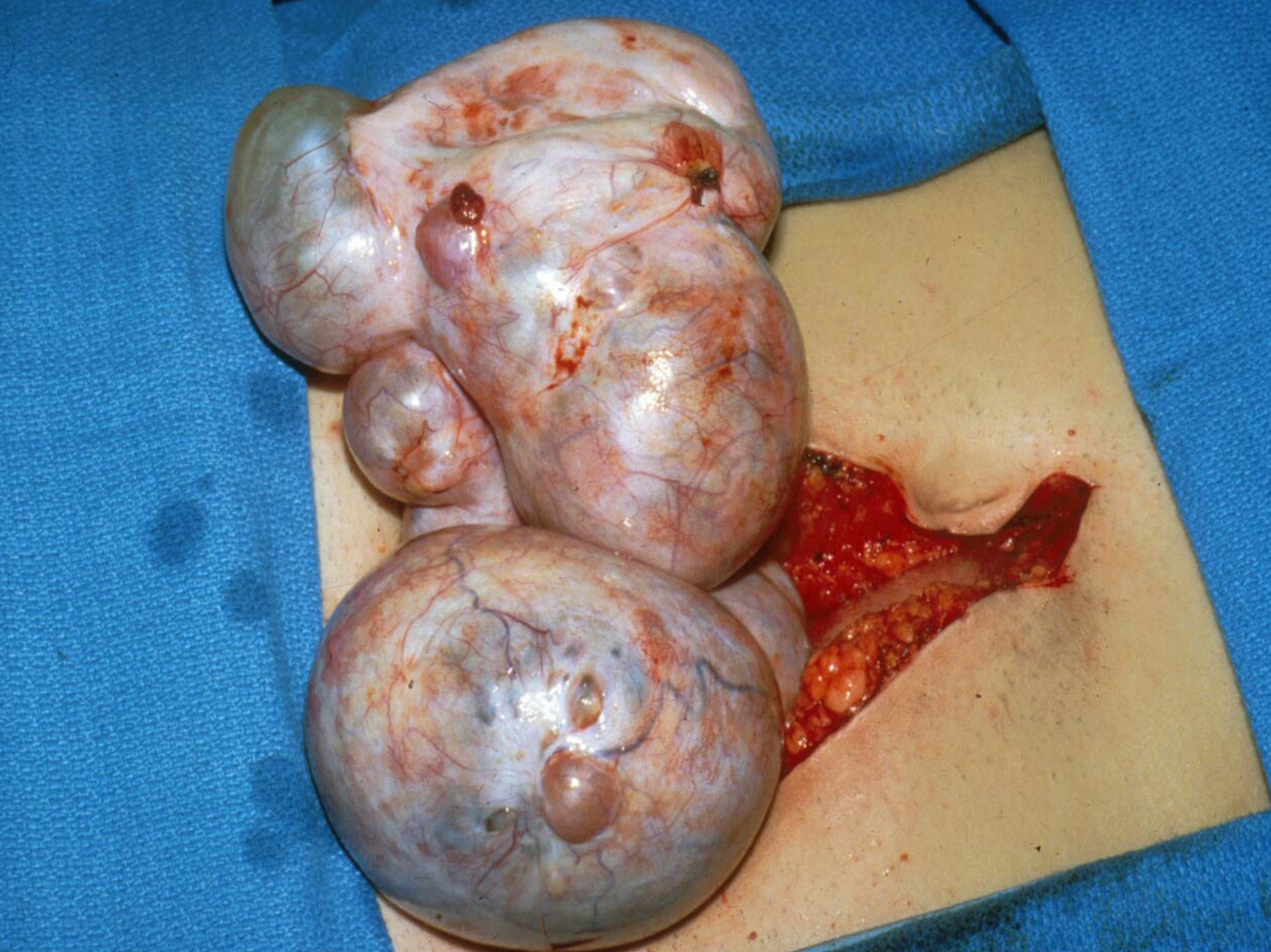
- Screening done in asymptomatic patients
- Early detection is accomplished when patients have minimal disease
- Recognition of early symptoms may result in earlier diagnosis



FIGO Stage IA

FIGO Stage IIIC

Early Detection of Ovarian Cancer



Ovarian Cancer

How is ovarian cancer treated?

- Most ovarian cancer requires several therapies
  - Surgery
  - Chemotherapy
  - Radiation therapy (rare)

Surgery for Ovarian Cancer

Goals

- Primary – establish diagnosis, staging, reduce tumor volume
- Secondary – assess response, repeat surgery for recurrent cancer
- Supportive and palliative care– relieve obstruction, alleviate ascites/pleural effusion, establish IV or IP access

Management of Early Stage Disease

Surgical staging is cornerstone

- Consider high risk factors – tumor grade, ascites, dense adhesions
- Chemo for patients with high risk factors even if early stage disease
- 90% 5 year survival if low risk, without treatment
- Recurrence rate up to 50% if high risk factors

Surgical Staging Guidelines

- At least two washings to detect floating cancer cells
- Careful evaluation of all organ surfaces
- Multiple biopsies of abdominal lining
- Biopsy any suspicious areas (including adhesions)
- Take sample of omentum (fatty apron)
- Biopsies of abdominal/pelvic lymph nodes
- TAH/BSO, excision of all masses (depending on fertility interests)

Management of Advanced Stage Disease

Surgery

- Resect majority or all of tumors, if feasible
- Largest unresectable mass determines stopping point
- Optimal surgery possible in 50-70% of patients with Stage III and IV disease
- Neoadjuvant approach: chemotherapy, followed by interval surgery, then more chemo

Management of Advanced Stage Disease

Surgical procedures used:

- TAH/BSO
- Omentectomy
- Pelvic and para-aortic lymphadenectomy
- Bowel resection
- Tumor debulking (peritoneal implants)
- More radical resection (splenectomy, pancreatectomy, diaphragm stripping, etc.)

Ovarian Cancer

Myth: Cancer cells grow like wildfire when exposed to air

Reality: Exposure to air has no effect on ovarian cancer cell growth

- Old wive's tale probably related to patients who had surgery for advanced, unresectable disease who died shortly after operation

Chemotherapy

What is chemotherapy?

- Chemotherapy drugs are usually given by vein into the blood system
- Kills cancer by stopping cell division and reproduction
- Cancer cells are more sensitive to chemo than normal cells
- Normal cells at risk for damage include all blood cells, hair cells, cells of digestive tract

Chemotherapy

Goals

- Adjuvant – eradicate or reduce remaining cancer cells after surgery, obtain remission or cure
- Salvage – treatment of recurrent disease, control symptoms, extend remission
- Neoadjuvant – chemotherapy given prior to surgery, reduce tumor volume to make surgery more feasible

Chemotherapy

Typical first-line treatment

- Carboplatinum and Taxol (paclitaxel)
- Outpatient treatment over 4-6 hours
- Response rate (total and partial) – 80-90%
- Neoadjuvant – chemotherapy given prior to surgery, reduce tumor volume to make surgery more feasible

Ovarian Cancer

Myth: Chemotherapy is worse than the disease itself

Reality: Ovarian cancer chemotherapy is very tolerable in 2004

- Drugs can prevent 80-90% of nausea and vomiting
- Immune-boosting drugs prevent or shorten chemotherapy-related infection risks

Ovarian Cancer

Myth: No-one survives ovarian cancer

Reality: Patients with Stage I ovarian cancer have a 5-year survival between 70-80%

- Patients with ovarian cancer have a variable prognosis which depends on stage, grade, and histology

Ovarian Cancer: Survival by Stage

Stage	Number (%)		5-yr Survival
Ia	845(13.8)		83.5
Ib	188 (3.1)	(26.8)	79.3
Ic	606 (9.9)		73.1
IIa	140 (2.3)		64.6
IIb	272 (4.4)	(12.2)	54.2
IIc	336 (5.5)		61.3
IIIa	171 (2.8)		51.7
IIIb	366 (6.0)	(39.9)	29.2
IIIc	1903 (31.1)		17.7
IV	1291 (21.1)	(21.1)	14.3
Total	6118		

FIGO 1994 Data

Ovarian Cancer

Why is it important to have a positive attitude?

- Easier to cope with serious challenges
- Better able to accept help from family and friends
- Helps maintain perspective
- Realization that every day is a gift
- Hope is important

Ovarian Cancer

Can you prevent ovarian cancer?

- Oral contraceptives decrease risk 50%
- Pregnancy decreases risk 30-60%
- Tubal ligation (or any Gyn surgery) decreases risk (unknown quantity)
- Prophylactic ovarian removal (98% effective)

Conclusions

- Ovarian cancer is a heterogeneous group of tumors with differing behaviors and survival
- Diagnosis often difficult due to vague, nonspecific symptoms
- Surgery is the cornerstone of treatment, followed by chemotherapy
- Overall survival has steadily improved due to innovations in surgery and chemotherapy
- Greatest impact in survival will come with early detection

References

- Myths & Facts about Ovarian Cancer. M. Steven Piver, M.D. and Gamal Eltabbakh, M.D., 3rd Edition, 2002.
- Ovarian.org (National Ovarian Cancer Coalition)
- Oncolink.org (University of Pennsylvania)
- Cancer.org (National Cancer Institute home page)